MUTATIONS RESPONSIBLE FOR OSTEOGLOPHONIC DYSPLASIA INCREASE THE BASELINE SIGNALING OF FGFR1

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Osteoglophonic dysplasia is a rare genetic disorder found in about ten families in the world. Patients with this disease show phenotypic characteristics such as craniosynostosis, rhizomelic dwarfism, and non-ossifying bone lesions. In these patients, three different mutations (N330I, Y374C and C381R) have been found in the fibroblast growth factor receptor 1 (FGFR1) gene. Purpose of this study was to determine the level of cellular signaling by mutant FGFR1. Wild-type FGFR1 was cloned in an expression vector. Expression vectors harboring mutant FGFR1 were generated by site-directed mutagenesis. The expression vectors were transfected into human embryonic kidney cells (HEK293). Total RNA was extracted from the transfected cells. Quantitative real-time PCR was conducted to determine the level of FGFR1 signaling using EGR-1 as the downstream mediator of the FGFR1 signal and β-actin as an internal control for normalization. Compared to the wild-type FGFR1, C381R mutant had approximately...
19-fold higher signaling, and N330I had approximately 10-fold higher signaling. However, Y374C had signaling comparable to wild-type. In summary, these results indicate that N330I and C381R are activating mutations, which increase the baseline activity of FGFR1. Although the Y374C mutant did not increase FGFR1 signaling, it may show inappropriate signaling only in the absence of ligands.